Remarks/Arguments

The foregoing amendments to the claims are of a formal nature, and do not add new matter. Claims 124, 129-131, 135-145 were pending in this application. Claim 139 has been amended to more clearly define what the Applicants consider is their invention. New claims 146-150 have been added which rely on assay 94: inhibition of the uptake of glucose or FFA (free fatty acids) by adipocyte cells. Accordingly, Claims 124, 129-131, 135-145 and 146-150 are now pending in this application. The previous rejections are traversed and discussed as applied to the new claims.

Continuity

As asserted previously, Applicants believe they are entitled to an effective filing date of at least **June 23, 1999** based on the gene amplification assay for claims 124, 129-131 and 135-145.

Further, Applicants rely on assay 94 (detection of polypeptides that affect glucose or FFA uptake by primary rat adipocytes; Example 158, page 530 of the specification) for patentable utility of nucleic acids encoding PRO1182, which was first disclosed in International Application PCT/US00/08439, filed March 30, 2000, priority to which has been claimed in this application. Hence, Applicants believe that they are entitled to an effective filing date of at least **March 30, 2000** for claims 124, 129-131, 135-138 and new claims 146-150.

Claim Rejections – 35 USC § 101 and §112, first paragraph

Claims 119-126, 129-131 and 135-145 were rejected under 35 U.S.C. §101 for lack of utility.

Claims 119-126, 129-131 and 135-145 were further rejected under 35 U.S.C. §112, first paragraph allegedly since "the claimed invention was not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention".

In the previous response of December 20, 2004, Applicants had canceled claims 119-123, 125 and 126, and had amended claim 124 to remove references to polypeptides. Applicants had also submitted a Declaration by Audrey Goddard, Ph.D. to show that a 2-fold increase in DNA copy number is considered significant and had asserted that thus,

one skilled in the art would know that the claims had utility in the detection of squamous lung carcinomas. In this response, Applicants have further amended claim 139 to recite "(a)n isolated nucleic acid molecule consisting of a fragment of the nucleic acid sequence of SEQ ID NO: 356 or a complement thereof.... that specifically hybridizes under stringent conditions" to more particularly claim what the Applicants consider is their invention. Accordingly, Applicants submit that claims 124, 129-131 and 135-145 have patentable utility based on results in the gene amplification assay.

New claims 146-150 rely on assay 94 (inhibition of the uptake of glucose or FFA (free fatty acids) by adipocyte cells) for patentable utility. The adipocyte glucose/FFA uptake assay is designed to determine whether a polypeptide is capable of modulating, either positively or negatively, the uptake of glucose or free fatty acids by adipocyte cells. The assay identifies polypeptides that are useful for treating disorders wherein stimulation or inhibition of glucose uptake by adipocytes is therapeutically effective. Examples of such disorders include, but are not limited to, obesity, diabetes, and hyper- or hypo-insulinemia.

The adipocyte glucose/FFA assay of the instant application is performed as follows: primary rat adipocyte cells are plated on a 96 well plate and incubated overnight with media supplemented with PRO1182 polypeptide. After the initial overnight incubation, samples of the media are taken at hour 4 and hour 16 and residual glycerol, glucose and FFA are measured. After the hour 16 sample is taken, insulin is added to the media and the adipocytes are allowed to incubate for an additional 4 hours. After this final 4 hour incubation, another sample is taken and residual glycerol, glucose and FFA is measured again. As a control, identical incubations and samplings are performed on cells that have been incubated overnight in media initially supplemented with insulin rather than PRO1182 polypeptide. Results are scored as positive in the assay if the uptake is greater than 1.5 times (stimulatory) or less than 0.5 time (inhibitory) the uptake of the insulin control. As PRO1182 resulted in less than 0.5 the uptake of the insulin control, PRO1182 tested positive as an inhibitor of glucose/FFA uptake in adipocyte cells.

The glucose/FFA uptake assay, as described in Example 158 of the instant application, was a "well-established assay" around the effective filing date of March 30, 2000. Applicants show, by discussing prior publications that were available in the art around the effective filing date of March 30, 2000, that there was an art recognized nexus between proteins that tested

positive in the adipocyte glucose/FFA assay and certain disease states. For example, it was well known in the art around March 30, 2000 that, increased glucose uptake by adipocyte cells was the hallmark of a number of therapeutically effective agents, such as troglitazone and poiglitazone. (Tafuri, *Endocrinology*, 137(11): 4706-4712 (1996); Sandouk, *et al.*, *Endocrinology*, 133(1):352-359 (1993) - copy to be enclosed with IDS to be filed shortly). Both troglitazone and poiglitazone are members of the thiazolidinedione class of compounds and have been used to effectively treat noninusulin-dependent diabetes mellitus (NIDDM), the most common form of diabetes. Both compounds were shown to function, at least in part, by increasing the number of cellular glucose transporters in order to facilitate increased glucose uptake.

Further, vanadium salts were considered to be a potential treatment for diabetes, and several clinical trials had already been performed as of the effective filing date of Msrch 30, 2000 (see page 26617, right column, Goldwaser *et al.*, *J. Biol Chem.*, 274(37):26617-26624 (1999) - copy to be enclosed with IDS to be filed shortly). Using the rat adipocyte culture system, similar to the system disclosed in the instant application, Goldwaser *et al.*, showed that vanadium ligand l-Glu (γ)HXM potentiates the capacity of free vanadium ions to activate glucose uptake and glucose metabolism in rat adipocytes *in vitro* by 4-5 folds and to lower blood glucose levels in hyperglycemic rats *in vivo* by 5-7 folds. Similar assays were commonly used to identify potential anti-diabetic agents and to examine the regulatory mechanisms of important molecules involved in fat cell metabolism.

Further, Mueller *et al.*, who were interested in determining the influence of glucose uptake on leptin secretion, employed essentially the same assay to measure changes in glucose uptake after insulin exposure. (Mueller *et al.*, *Endocrinology*, 139(2): 551-558 (1998) - copy to be enclosed with IDS to be filed shortly). Figure 1A showed the glucose concentrations in medium from 0-96 hours from isolated rat adipocytes in primary culture with various insulin concentrations. As indicated by the decrease in glucose in the medium in the Figure, Mueller *et al.* suggested that insulin produced a concentration-dependent increase in glucose uptake by the cultured adipocytes. Based on these experimental results, the authors stated that insulin increased leptin secretion over 96 hours, and that the increase in leptin was more closely related

to the amount of glucose taken up by the adipocytes than to the insulin concentration, suggesting a role for glucose transport and/or metabolism in regulating leptin secretion. (See Abstract).

Using the same assay system, Mueller *et al.* further studied the effect of two well-known anti-diabetic agents, metformin and vanadium, on leptin secretion. These agents were known to enhance glucose uptake. (Muller *et al.*, *Obesity Research,* 8(7): 530-539 (2000) - copy to be enclosed with IDS to be filed shortly). Mueller's experimental data indicated that both metformin and vanadium increased glucose uptake and inhibited leptin secretion from cultured adipocytes.

The studies discussed above clearly establish that the glucose/FFA uptake assay, as described in the instant application, is a well-established assay useful for identifying therapeutic agents for treating metabolic diseases such as obesity, diabetes, hyper- or hypo-insulinemia. Thus, Applicants respectfully submit that at the effective filing date of the present application, one skilled in the art would have reasonably accepted that molecules activating glucose uptake, like PRO1182, would find real-life utilities in the treatment of metabolic diseases such as diabetes, obesity and related diseases.

In view of the above, Applicants respectfully submit that the specification discloses at least one credible, substantial and specific asserted utility for the polypeptide PRO1182. Accordingly, the Examiner is requested to reconsider and withdraw the present rejection under 35 U.S.C. §101.

Claim Rejections - 35 USC § 112, first paragraph- Written Description

Claims 119-123 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time of filing, had possession of the claimed invention. Applicants respectfully traverse this rejection to the pending claims.

In view of the cancellation of claims 119-123 without prejudice or disclaimer, this rejection is moot and should be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2730P1C64).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: February 28, 2005

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